

• §Appl. No. 09/950,003
Amdt. dated June 29, 2006
Reply to Office Action of, May 2, 2006

REMARKS

¹ Claims 14-34, 38-53, 56-62, 64, 66, 68 and 70 are now pending.

Interview Summary

As discussed during the Interview of February 23, 2006, Claims 12-13 and 71-77 have been cancelled and an analysis has been provided to illustrate that the claims pending in this application are not supported by the disclosure within co-pending application 10/240,606. The same is true for Italian priority document MI2000A000655; however, Applicants have elected not to formally disclaim priority to Italian Application No. MI2000A000655 for the reasons indicated below.

Claim Amendments After Final

The amendments above are appropriate under 37 C.F.R. §1.116 and should be entered. The amendment to claims 38 and 56 change the range of sulfate groups in iduronic units for R₁ to "from about 25 to about 30%." This range falls within the originally recited ranges and is supported by the specification as filed, particularly the disclosure which appears on page 21, line 27. The amendments to claims 38 and 50 correct clerical errors and the cancellation of claims 12-13 and 71-77 were discussed during the interview. These amendments do not raise new issues which would require additional search or consideration and so are appropriate under 37 C.F.R. §1.116.

Interference between Co-Pending Applications Serial Nos. 11/030,156 and 10/240,606

Original claims 1-11, which were cancelled with the response filed on January 21, 2005, have been presented in co-pending application Serial No. 11/030,156, filed on January 7, 2005. Claims 1-11 in co-pending application 11/030,156 are identical or substantially identical to claims 1-11 of co-pending application 10/240,606, of which Claims 1-6, 8 and 10 have been allowed. Co-pending Application 11/030,156 claims priority to this application, parent application 09/738,879 and Italian Application No. MI2000A000655. The U.S.P.T.O. cannot properly permit the allowed claims of the '606 application to issue without first declaring an interference with Serial No. 11/030,156.

The Priority Claim to Italian Application MI2000A000655:

This application has been limited to claims which cannot obtain the benefit of the priority document, Italian Application MI2000A000655. In contrast, claims 1-11 of co-pending Application 11/030,156 are completely supported by Italian Application No. MI2000A000655 and are entitled to the priority date of March 30, 2000. Applicants have not formally withdrawn the claim to priority to the Italian Application No. MI2000A000655 in the present application, as discussed during the interview, so as to maintain continuity for the priority claim made in co-pending application 11/030,156.

It is alleged the priority claim to Italian Application No. MI2000A000655 cannot be granted in that the instant application only names two of the three inventors named in the Italian application. Since the disclosure within Italian Patent Application No. MI2000A000655 does not support the claims now pending in this application; this issue is moot with respect to the pending claims. In an interference with the '606 application, the propriety of the priority claim in the '156 application will be established.

Italian Application No. MI2000A000655 and International application WO 01/72848

The priority claim to the Italian Application for the pending claims does not provide a priority date of March 30, 2000. Therefore, Italian Application MI2000A000655, which published on December 14, 2000 is, prima facie, a reference under 35 U.S.C. §102(a) and International application WO 01/72848, filed on March 27, 2001 is, prima facie, a reference under 35 U.S.C. §102(e) for the new subject matter added and claimed herein.

However, in fact the documents are not prior art references under 35 U.S.C. §102(a) and 35 U.S.C. §102(e) because their relevant disclosures were invented only by the two inventors of the above-identified application. However, whether these documents are prior art references against the pending claims is irrelevant in that the subject matter defined by these claims is established herein as patentably distinct from the disclosures within these documents.

Double Patenting

Co-pending application 10/240,606 ('606) does not support claims 16-74 therein. Thus, there is no basis there for the rejection under 35 U.S.C. §101 made in this application.

Applicants have prepared a table ("Comparison Table") wherein:

- (1) the content of the '606 application is compared to the content of this CIP application to identify the additional disclosure which was added to support the pending claims;
- (2) disclosures which support unique elements of the methods and compositions now claimed have been identified with an asterisk ("*"), and
- (3) disclosures which support elements within specific claims have been identified with the claim number.

The comparison was made using corresponding published U.S. Patent Applications wherein each paragraph is numbered. U.S. Published Application 2004/0196994A1 was used for U.S. Patent Application No. 10/240,606 and U.S. Published Application 2002/0062019 A1 was used for this CIP Application (U.S. 09/950,003). In the first two columns of the table, paragraphs or groups of paragraphs within the '606 and '003 applications having identical disclosure are put in the same row. A blank row in any column for a given application indicates it does not contain any disclosure which corresponds to that particular paragraph found within the other application. Paragraphs containing generic disclosure relevant to unique elements of the methods and compositions claimed are identified with an asterisk (*) in the column with the heading "Claims". Where a paragraph contains disclosure relevant to elements of a particular claim, the claim has been identified in the column with the heading "Claims".

As can be seen from the Comparison Table, this CIP application contains a significant amount of additional disclosure within the "Detailed Description" and the examples. More importantly, the '606 application does not contain any of the additional disclosure which is relevant to the subject matter of the pending claims, either generically (marked by an asterisk) or specifically (identified by claim number). The lack of support for the method claims and composition claims is discussed more particularly below.

Method Claims 14-34:

A feature which distinguishes the process for preparing K5 glycosaminoglycans described in claims 14-34 from the methods described in the '606 application (and Italian Application MI2000A000655) is the selective O-desulfation step (step iv). This step comprises "treating the over sulfated product obtained at the end of step (iii) with a mixture of methanol/dimethyl sulfoxide for a period of time of from 135 to 165 minutes." The '606 application describes methods of preparing glycosaminoglycans but makes no reference to these specific conditions for the selective O-desulfation step employed in the methods of claims 14-33 of treating the over-sulfated product for a period of 135 to 165 minutes. General reference to methods for preparing glycosaminoglycans is made in paragraphs 0009-0017 of '606 with a general reference to selective O-desulfation in paragraph 0015. A detailed description of the process is provided in paragraphs (0018)-(0071) of the '606 application. The portion which is relevant to selective O-desulfation is given at paragraphs 0056-0059. Here it is stated the product obtained from step d) "is treated with 20-2000 ml of DMSO/methanol (9/1 V/V) solution and the obtained solution is kept at 45 to 90°C for 1-8 hours." No preferred range is given and there is no disclosure for supporting the range recited in claims 14-33 of 135 to 165 minutes. The examples provide for O-desulfation steps with a duration of 3.5 hours (Examples 1 and 2); 4 hours (Examples 3, 7 and 10); 2 hours (Examples 4 and 11) and 3 hours (Examples 5, 8 and 9). No mention is made of a range corresponding to that recited in claims 14-33.

The methods of claims 14-33 are supported by the added disclosure as it appears in paragraphs 0099-0138 of the present application, as well as in examples 12 and 17. As shown in the Comparison Table, the '606 application provides no corresponding disclosure. In that the '606 application provides no disclosure that supports claims 14-33, these claims cannot be legitimately maintained in the '606 application. Therefore, there is no proper basis for the double patenting rejection of claims 14-33 made in this application and this rejection should be withdrawn.

Claims 38-53, 56-62, 64, 66, 68 and 70

The glycosaminoglycans of claims 38-53 are distinguished from those disclosed in the '606 application (and Italian Application MI2000A000655) by the sulfation pattern defined

by variables R, R₁, R₂ and R₃ of formula I. The '606 application provides no disclosure which describes or which would lead to the glycosaminoglycans of these claims.

A discussion of the prior art in '606 application makes reference to sulfate groups in paragraph 0003. The summary of the invention within the '606 application indicates that the glycosaminoglycans are of a particular molecular weight with chains having high affinity for ATIII and having high anticoagulant/antithrombotic activity. However, there is no indication that the degree of sulfation or that the position of the sulfate groups is relevant to the anti-coagulant and antithrombotic activity. General reference is made to the characterization of the glycosaminoglycans by proton and carbon 13 NMR and by biological tests such as anti Xa, APTT, HCII, Anti IIa and affinity for ATIII¹. (See paragraph 0072) Sulfate content of the disaccharides is discussed in paragraphs 0055, 0064 and 0069. However, no mention is made of glycosaminoglycans having a sulfate distribution as required for claims 38-53.

The products obtained in examples 1-11 of '606 are characterized by their anticoagulant and antithrombotic activity and molecular weight. There is no indication of the sulfate content or the distribution of the sulfate groups on the final products.

In contrast, the glycosaminoglycans of claims 38-53 are supported by paragraphs 0139-0170 of the present application and claims 56-62, 64, 66, 68 and 70 are supported by paragraphs 0174-0204 of the specification. Additional support is found in the examples, more particularly, examples 12 and 17.

It is clear that the glycosaminoglycans of claims 38-53 herein and the methods and compositions which employ them (dependent claims 56-62, 64, 66, 68 and 70) are not supported by any paragraph of the '606 application. Therefore, the rejection of these claims under 35 U.S.C. §101 cannot be properly maintained in this application and should be withdrawn.

Declaration under 37 C.F.R. 1.132

The subject matter claimed herein is patentably distinct from the disclosures in the Italian application and WO 01/72848.

These claims are to new glycosaminoglycans having a distinct sulfation pattern, which show higher antithrombotic activity than the compounds disclosed in Italian application MI2000A000665 and WO 01/72848. The Rule 132 declaration of Dr. Oreste

illustrates that glycosaminoglycans having a sulfation pattern as defined in claims 38-56 have a high affinity for ATIII. These glycosaminoglycans retain their high activity once depolymerized. The high activity of these glycosaminoglycans is unexpected and significantly advantageous over the glycosaminoglycans of Italian application MI2000A000665 and WO 01/72848. Claims 38-53 define these patentably distinct glycosaminoglycans through their sulfation patterns. Methods and compositions which employ these glycosaminoglycans (claims 56-62, 64, 66, 68 and 70) are also correspondingly patentably distinct over the disclosures within Italian application MI2000A000655 and WO 01/72848.

The claims of this application are also to new methods for producing these K5 glycosaminoglycans. Such methods are also patentably distinct over the methods disclosed in the Italian application and WO 01/72848. The steps of the claimed methods [step (i)- step (vi)] correspond in general to the methods described in Italian application MI2000A000655 and WO 01/72848 [step a)-step g)], except for the O-desulfation step. A comparison is made below.

Step a) ---	preparation of the K5 polysaccharide		
Step b) ---	Step (i)	N-deacetylation/N-sulfation of the polysaccharide K5	
Step c) ---	step (ii)	C5 epimerization	
Step d) ---	step (iii)	Supersulfation/oversulfation	
Step e) ---	step (iv)	Selective O-desulfation*	
Step f) ---	step (v)	optional selective 6-O-Sulfation	
Step g) ---	step (vi)	N-sulfation	

The new methods are distinguished from the methods described in Italian application MI2000A000655 and WO 01/72848 in that the O-desulfation step is limited to 135-165 minutes. As discussed above, Italian application MI2000A000655 and WO 01/72848 disclose a time period for the O-desulfation ranging from 1-8 hours and specific reaction durations of 2, 3, 3.5 and 4 hours. There is no suggestion of preferred time periods or that the duration of

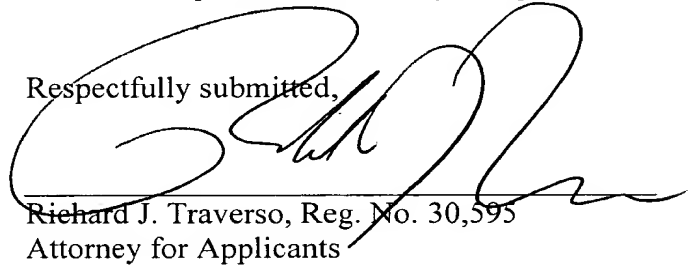
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• §Appl. No. 09/950,003
Amdt. dated June 29, 2006
Reply to Office Action of, May 2, 2006

the O-desulfation reaction affects the structure (sulfate distribution) and ultimately the antithrombotic activity of the compounds produced.

The accompanying declaration of Dr. Oreste illustrates there are significant unexpected advantages in preparing glycosaminoglycans under selected conditions where the duration of the selective O-desulfation step is limited to 135-165 minutes such that the methods of claims 14-33 are unobvious in view of Italian Application MI2000A000665 and WO01/72848.

In view of the above, favorable reconsideration is courteously requested. If there are any remaining issues which can be expedited by a telephone conference, the examiner is courteously invited to telephone counsel at the number indicated below. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No.: **MARGI-0027-P01**

Date: **June 29, 2006**



Comparison Table

Paragraph by paragraph comparison of US Applications Publications Nos. **2004/0146994A1** (US 10/240,606) and **2002/0062019** (US 09/950,003).

2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
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[0001]	[0002]	
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[0011]	[0038]	
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[0014]	[0041]	

2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
[0015]	[0042]	
[0016]	[0043]	
[0017]	[0044]	
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[0028]	[0051](partial corresp.)	
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2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
[0061]	[0079]	
[0062]	[0080]	
[0063]	[0081]	
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	[0092] - [0093]	
Table 1	Table 1 + references	
[0075] (Ref.)		
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[0077] (Ref.)		
[0078] (Ref.)		
[0079] (Ref.)		
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[0081]	[0094]	
[0082]	[0095]	
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[0084]	[0097]	
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	[0099]	* Claim 14
	[0100]	* Claim 15
	[0101]	
	[0102]	* Claim 16
	[0103]-[0107]	Claims 17-34
	[0108]	* Claims 17-34
	[0109]- [0110]	Claims 17-34
	[0111]	Claim 18
	[0112]	
	[0113]	Claim 19
	[0114]	Claims 20, 23 & 24
	[0115]- [0116]	
	[0117]	* Claims 26 & 27

	[0118]	
	[0119]	Claims 30 & 31
	[0120]- [0125]	
	[0126]	Claims 32, 33 & 34
	[0127]- [0131]	
	[0132]	*
	[0133]- [0134]	
	[0135]	*
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	[0139]- [0146]	Claims 38-43
	[0147]	
	[0148]	Claim 41
	[0149]	Claim 42
	[0150]	Claim 43
	[0151]- [0154]	* Claims 44-47
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	[0156]- [0158]	* Claims 44-47
	[0159]- [0160]	
	[0161]	Claim 48
	[0162]	Claim 49
	[0163]- [0165]	* Claims 50-53
	[0166]	* Claims 50-53
	[0167]- [0170]	* Claims 50-53
	[0171]- [0173]	
	[0174]- [0180]	Claim 56
	[0181]- [0186]	
	[0187]	Claims 57 & 58
	[0188]- [0195]	
	[0196]- [0202]	Claims 59-62
	[0203]	Claims 64 & 68
	[0204]	Claims 66 & 70

2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
[0085] Introd. Examl	0207] Introd. Examl	
[0086]	[0208]	
[0087]		
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2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
[0126]	[0233]	
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	[0272]	
	[0273]-[0274]	
		Claims 14-29
		*

2004/0146994A1 (US 10/240,606)	2002/0062019 (US 09/950,003)	US 09/950,003 Claims
	[0275]	
	[0276]	Claims 38, 50, 53
	[0277]-[0281]	Claims 30-31
	[0278]	* Claims 44-47
	[0282]	
	Table 3	
	[0283]	
	[0284]	* Claim 50
	[0285]-[0287]	